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EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	

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12

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/828,505	RAZ ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *8,9,17 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,10-16,19-22,25,26 and 29-32* is/are rejected.

7)☒ Claim(s) *2,3,23,24,27 and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8 and 9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-32 are pending in the present application.

Applicants' election with traverse the invention of Group I (claims 1-7, 10-16 and 19-32) in Paper No. 11 is acknowledged. Applicants further elected the group of claims drawn to "plant allergen" with traverse. Additionally, Applicants elected with traverse the following species: (a) "ragweed" as a species of plant allergen; and (b) "AACGTT" as a species of an unmethylated 5'-CG-3'. With respect to restriction requirement for the plant allergen species, Examiner has decided to withdraw this species restriction requirement. Therefore, both ragweed and grass pollen plant allergens are examined herein.

With respect to the Group restriction requirement, Applicants argue that it would not be undue burdensome to perform a search on all the claims 1-32 together. Additionally, Applicants argue that MPEP 803 states that if search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions. Applicants' arguments are respectfully found to be unpersuasive because there is no extensive overlap in the searches for a polynucleotide vaccine encoding a plant allergen, a food allergen, a latex allergen, a house dust mite allergen, a cockroach allergen, let alone for a polynucleotide vaccine encoding a pathogenic bacterium or a pathogenic virus or a pathogenic parasite. These encoded allergens and pathogenic bacterium, virus and parasite do not share a substantial common core structure or element among themselves. Additionally, depending on the nature of the encoded

antigen whether it is an allergen or a pathogenic antigen, different types of immune responses to the antigen in the host are desired. For example, suppression of the IgE production against an allergen is desired whereas this suppression is not required in the situation of a pathogenic antigen. Therefore, different considerations are required to evaluate for methods of modulating or eliciting an immune response to an antigen as claimed. Thus, it appears that it would be undue burden for the Examiner to search and/or consider the patentability of all the claims within a single patent application. Furthermore, each patent application is entitled to a single distinct or independent invention.

With respect to the species restriction requirement, Applicants argue that the claims are directed to a reasonable number of species, and therefore the species requirement is not proper. Applicants' argument is not persuasive because it is undue burden for the Examiner to search for 65 different sequences containing the CpG motif. 65 distinct sequences are not deemed to be a reasonable number of species.

Therefore, restriction for examination purposes as indicated in the Office Action is proper, and this is made FINAL.

Therefore, claims 8-9 and 17-18 are withdrawn from further consideration because they are drawn to non-elected inventions.

Accordingly, claims 1-7, 10-16 and 19-32 are examined on the merits herein.

Claim Objections

Claims 1-5, 10-13, 15-16, 19-21, 26-29 and 31-32 are objected because they contain embodiments of non-elected inventions and/or species.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed."Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

With respect to the elected invention, Applicant's invention is drawn to a method for modulating an immume response or eliciting an immune response to a plant allergen, said method comprises administering to a subject an immunostimulatory nucleotide sequence (ISS). As defined by the present application, ISS is referred to a

polynucleotide that comprises at least one immunomodulatory moiety (see page 9, top of the fourth paragraph). However, apart from disclosing that the ISS comprises at least one hexamer having the unmethylated CpG motif, the specification fails to teach any other immunostimulatory polynucleotide sequences containing any other immunomodulatory moieties. Additionally, the state of the art was such that at the effective filing date of the present application, non-CpG motif containing immunostimulatory polynucleotide sequences that have any beneficial uses in modulating or eliciting an immune response to any allergen are not known. Additionally, the instant specification fails to teach a representative number of species for a broad genus of immunomodulatory moiety present in the ISS as claimed. The claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of Applicants' filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure or critical elements of non-CpG motif containing immunostimulatory polynucleotide sequences to be utilized in the methods as claimed. Therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and

reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-16 and 19-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of eliciting a Th1 immune response to a plant allergen in a subject comprising co-administering to the subject an effective amount of a polynucleotide vaccine comprising a nucleic acid sequence encoding the allergen, wherein the nucleic acid sequence encoding the allergen is modified by deletion of a native signal sequence, and an effective amount of an immunostimulatory nucleotide sequence (ISS) containing at least one unmethylated CpG motif, does not reasonably provide enablement for a method of modulating or eliciting any immune response to a plant allergen in a subject in the absence of or without the co-administration of an immunostimulatory nucleotide sequence (ISS)

containing at least one unmethylated CpG motif in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

Claims 10-14 and 19-21 are drawn to a method for modulating an immune response to an antigen comprising administering to a subject a polynucleotide vaccine of claim 1 in an amount effective to modulate an immune response to the antigen. Claims 15-16 are directed to a method for eliciting an immune response to an antigen comprising administering to a subject a polynucleotide vaccine of claim 1 in an amount effective to elicit an immune response to the antigen.

With respect to the elected invention (plant allergens), the instant claims encompass a method for modulating and eliciting any immune response to a plant allergen comprising administering to the subject the polynucleotide vaccine of claim 1. Additionally, the claimed methods are not limited to the co-administration of the polynucleotide vaccine and an immunostimulatory nucleotide sequence to the subject, and wherein the immunostimulatory nucleotide sequence contains any immunomodulatory moiety encompassing both CpG and non-CpG motifs. The instant

specification is not enabled for such a broadly claimed invention for the reasons discussed below.

(a) The breadth of the claims. The claims encompass a method for modulating and eliciting any immune response to a plant allergen comprising administering to the subject the polynucleotide vaccine of the presently claimed invention, wherein the immunostimulatory nucleotide sequence containing any immunostimulatory motif is not necessarily present in the polynucleotide vaccine encoding the plant allergen nor is it required to be co-administered with the polynucleotide vaccine.

(b) The state of the art. At the effective filing date of the present application, it is known that the presence of an immunostimulatory sequence containing a CpG motif within an expression vector encoding an allergen or co-injected with a vector encoding an allergen or together with an allergen is important for shifting the immune response in a subject from a Th2 immune response to a Th1 immune response, which is beneficial for the treatment of allergy (Roman et al., Springer Seminars in Immunopathology 19:223-232, 1997; IDS; Krieg et al., U.S. Patent No. 6,207,646; Carson et al., U.S. Patent No. 5,849,719).

(c) The amount of direction or guidance presented. Apart from the exemplification showing that upon co-administration of the immunostimulatory sequence of SEQ ID NO:1 containing the AACGTT motif with the plasmid pNDKm/hssHAΔ36Amb a1 encoding a ragweed allergen into mice that were sensitized to Amb a1, a significant reduction of Amb a1-specific IgE was obtained at week 8 following subsequent

challenges (example 6), the instant specification fails to provide sufficient guidance for a skilled artisan on how to attain a similar reduced Amb a1-specific IgE and/or a shift in the immune response in a subject from a Th2 immune response to a Th1 type immune response which is beneficial for the treatment of allergy in the absence of any immunostimulatory sequence or wherein the immunostimulatory sequence is not co-administered together with a polynucleotide encoding the allergen. Nor does the present disclosure teach the elicitation of any immune response to an allergen or modulate any immune response to an allergen at will at any time under any conditions, other than a shift in a Th2 immune response to a Th1 type immune response in the treated subject. Additionally, the instant specification fails to provide sufficient guidance for a skilled artisan on how to make and use an immunostimulory nucleotide sequence containing any immunostimulatory moiety (including non-CpG motifs) to elicit or modulate an immune response that is beneficial for treating a subject that is sensitized to plant allergens. Since the prior art at the effective filing date of the present application as discussed above does not provide such guidance, it is incumbent upon the present application to do so. Otherwise, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

(d) The unpredictability of the art. The physiological art is recognized as unpredictable (MPEP 2164.03), let alone for modulating or eliciting any type of immune response to an allergen in a subject to attain desired prophylactic and therapeutic effects. Furthermore, with respect to DNA vaccines containing the CpG motif McCluskie et al. (Crit. Rev. Immunol. 19:303-329, 1999; IDS) have noted that the route

of administration and DNA doses as well as other factors such as the antigen, the dose of antigen, the co-expression of cytokines, and whether other adjuvant is used are also involved in determining the types of host immune responses elicited (page 313, see the section titled "Role of CpG immunostimulatory sequences). As such, with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for one skilled in the art to make and use the full scope of the methods as claimed.

As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictagle factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues discussed above, the unpredictability of the physiological art, particularly the genetic immunization art for treatment of allergy, and the breadth of the instant claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 6-7 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Rogers et al. (U.S. Patent No 5,776,761).

Claims 1 and 6 are drawn a polynucleotide vaccine comprising a nucleic acid sequence encoding a plant allergen, wherein the nucleic acid sequence encoding the allergen is modified by deletion of a native signal sequence. Claim 22 is directed to a polynucleotide vaccine comprising a nucleic acid sequence encoding an Amb a1 allergen modified by deletion of a native Amb a1 signal sequence. It is noted that for composition claims, the intended use is not given any patentable weight in light of the prior art.

Rogers et al. disclose cDNAs encoding Amb al allergic proteins or peptides (do not contain native signal peptide) from ragweed, as well as expression vectors comprising the same for expression all or a portion of the Amb al allergic proteins in cultured host cells (see abstract, col. 19, lines 36-47, and the claims). The teachings of Rogers et al. meet all the limitation of the instant claims. Therefore, Rogers et al. anticipate the instant claims.

Claims 1 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Singh et al. (U.S. Patent No 5,965,455).

For composition claims, the intended use is not given any patentable weight in light of the prior art.

Singh et al. disclose nucleic acid sequences coding for two ryegrass pollen allergen Lol p Ib family members, and fragments (do not contain native signal sequence) of the nucleic acid sequences coding for parts of Lol pIb that elicit an immune response in mammals such as the stimulation of minimal amounts of IgE, binding of IgE, eliciting the production of IgG and IgM antibodies (see abstract and col. 9, lines 6-10). Singh et al. further provide expression vectors comprising these nucleic acid sequences coding for at least one Lol p Ib ryegrass pollen allergen or at least one antigenic fragment thereof in cultured host cells, including mammalian host cells (see col. 11, lines 1-20). It should be noted that Sigh et al. teach that the expressed Lol p Ib proteins and fragments or peptides can be purified from host cells as well as from the cell culture medium (col. 12, lines 6-8). The teachings of Singh et al. meet all the limitation of the instant claims. Therefore, Singh et al. anticipate the instant claims.

Claims 1, 6-7, 10, 12-15 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Carson et al. (U.S. Patent 5,804,566).

Carson et al. teach the preparation of polynucleotides encoding for intact allergen, T cell epitope(s) of an allergen, and/or either engineered by means well-known in the art to be non-secreting (without native signal sequence for secretion). Exemplified encoded allergens include the highly abundant Antigen E (Amb a1) ragweed pollen allergen, white birch pollen (Betvl) and others (col. 21, lines 29-56). Carson et al. further teach a method of administering these polynucleotides to the skin or mucosa of the host, wherein the skin and mucosa have a high concentration of

resident antigen presenting cells relative to other host tissues, and wherein the encoded non-secreted allergenic antigens are expressed in the antigen presenting cells to activate Th1 lymphocytes while reducing antigen-stimulated IgE production in the host (see cols. 18-23 and the claims). The teachings of Carson et al. meet all the limitation of the instant claims. Therefore, Carson et al. anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 22 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Singh et al. (U.S. Patent No 5,965,455) in view of Zolotukhin et al. (J.

Virol. 70:4646-4654, 1996; IDS), Kim et al. (Gene 199: 293-301, 1997; IDS) and Rogers et al. (U.S. Patent No 5,776,761).

Singh et al. disclose nucleic acid sequences coding for two ryegrass pollen allergen Lol p Ib family members, and fragments (do not contain native signal sequence) of the nucleic acid sequences coding for parts of Lol pIb that elicit an immune response in mammals such as the stimulation of minimal amounts of IgE, binding of IgE, eliciting the production of IgG and IgM antibodies (see abstract and col. 9, lines 6-10). Singh et al. further provide expression vectors comprising these nucleic acid sequences coding for at least one Lol p Ib ryegrass pollen allergen or at least one antigenic fragment thereof in cultured host cells, including mammalian host cells (see col. 11, lines 1-20). It should be noted that Sigh et al. teach that the expressed Lol p Ib proteins and fragments or peptides can be purified from host cells as well as from the cell culture medium (col. 12, lines 6-8).

Singh et al. do not specifically teach the preparation of nucleic acid sequences coding for two ryegrass pollen allergen Lol p Ib family members, and their peptide fragments, wherein at least one codon of the nucleic acid sequences encoding the allergic antigens is modified to an analogous codon of a host species or human species. Nor does Singh et al. disclose any nucleic acid sequences encoding Amb a1 allergen.

At the effective filing date of the present application, Zolotukhin et al. already teach the efficient transduction and expression of the jellyfish *Aequorea victoria* green fluorescent protein (gfp) in human cell line 293 as well as *in vivo*, the change in codon usage within the gfp coding sequence is required because a set of isoacceptor tRNAs in

human cells is different from that used in jellyfish (see abstract). Additionally, Kim et al. also teach that in order to achieve high-level expression of heterologous gene in mammalian cells, codon optimization for the heterologous gene is required because codon bias has been observed in many species (see abstract). Furthermore, Rogers et al. already disclose cDNAs encoding Amb al allergic proteins or peptides (do not contain native signal peptide) from ragweed, as well as expression vectors comprising the same for expression all or a portion of the Amb al allergic proteins in cultured host cells (see abstract, col. 19, lines 36-47, and the claims).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the nucleic acid sequences encoding ryegrass pollen allergen Lol p Ib family members of Singh et al. by substituting codon bases of these nucleic acid sequences with analogous codon bases commonly used in host cells, including mammalian or human cells, in light of the teachings of Zolotukhin et al. and Kim et al.

One of ordinary skilled artisan would have been motivated to carry out the above modification in order to obtain an efficient and high level of expression of recombinant ryegrass pollen allergens in host cells in light of the teachings of Zolottukhin et al. and Kim et al.

Similarly, it would also have been obvious and within the ordinary level of skill for an artisan to modify the nucleic acid sequences encoding Amb al ragweed allergic proteins or peptides of Rogers et al. by substituting codon bases of these nucleic acid sequences with analogous codon bases commonly used human host cells in light of the teachings of Zolotukhin et al., Kim et al. and Singh et al. for an efficient and high

expression of recombinant Amb a1 ragweed allergic proteins or peptides in human host cells.

The modified nucleic acids as a result of the combined teachings of Singh et al., Zolotukhin et al., Kim et al. and Rogers et al. are indistinguishable from a polynucleotide vaccines of the instantly claimed invention. Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 6-7, 10-16, 19-22, 26 and 30-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (U.S. Patent No 6,207,646; IDS) in view of Carson et al. (U.S. Patent 5,804,566).

Krieg et al. disclose a composition comprising a plasmid including an immunostimulatory sequence comprising 5'-$X_1X_2CGX_3X_4$-3', wherein X_1X_2 are ApA and X_3X_4 are TpT, and an antigen in a pharmaceutically acceptable carrier, and wherein an antigen is encoded in a DNA vaccine and the antigen is an allergen (see claims 6-7, 10 and 11). The encoded allergen includes any plant allergen (see line 40 of col. 9 continues to line 4 of col. 10). Krieg et al. further teach a method for desensitizing a subject against the occurrence of an allergic reaction in response to a particular allergen comprising administering to the subject an effective dose of the immunostimulatory nucleic acid alone or in conjunction with an allergen, based on the ability of the immunostimulatory nucleic acid molecules to shift the immune response in a subject from a Th2 (which is associated with production of IgE antibodies and allergy) to a Th1 response (which is protective against allergic reactions) (see cols. 34-35, and claim 3).

Krieg et al. do not specifically teach that the DNA vector encoding the plant allergen does not contain a sequence encoding a native signal sequence of the plant allergen.

However, at the effective filing date of the present application, Carson et al. already teach the preparation of polynucleotides encoding for intact allergen, T cell epitope(s) of an allergen, and/or either engineered by means well-known in the art to be non-secreting (without native signal sequence for secretion). Exemplified encoded allergens include the highly abundant Antigen E (Amb a1) ragweed pollen allergen, white birch pollen (Betvl) and others (col. 21, lines 29-56). Carson et al. further teach a method of administering these polynucleotides to the skin or mucosa of the host, wherein the skin and mucosa have a high concentration of resident antigen presenting cells relative to other host tissues, and wherein the encoded non-secreted allergenic antigens are expressed in the antigen presenting cells to activate Th1 lymphocytes while reducing antigen-stimulated IgE production in the host (see cols. 18-23 and the claims).

Accordingly, it would have been obvious for an ordinary skilled artisan in the art to modify the composition and the method taught by Krieg et al. by using a polynucleotide encoding for an intact, non-secreted plant allergen such as Amb a1 ragweed allergen or its T cell epitope(s) for desensitizing a subject against the occurrence of an allergic reaction in response to Amb a1 in light of the teachings of Carson et al.

One of ordinary skilled artisan would have been motivated to carry out the above modification because Carson et al. specifically teach that to minimize, if not avoid, extracellular stimulation of IgE antibody formation against expressed allergen, the allergen-encoding polynucleotides administered will preferably be administered as part of a non-secreting recombinant expression vector (see col. 21, lines 57-61). One of ordinary skilled artisan would also have been further motivated to carry out the above modification for the encoded Amb al because it is the highly abundant Antigen E (Amb a1) ragweed pollen allergen that a sensitized subject would be in contact.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 26 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (U.S. Patent No 6,207,646; IDS) in view of Carson et al. (U.S. Patent 5,804,566) as applied to claims 1, 6-7, 10-16, 19-22, 26 and 30-32 above, and further in view of Zolotukhin et al. (J. Virol. 70:4646-4654, 1996; IDS), Kim et al. (Gene 199: 293-301, 1997; IDS).

The combined teachings of Krieg et al. and Carson et al. are presented above and applied as before. However, none of the references specifically teach that at least one codon of the nucleic acid sequence encoding the plant allergen is modified from a wild type sequence of the non-host species to an analogous codon of a host species.

However, at the effective filing date of the present application, Zolotukhin et al. already teach for efficient transduction and expression of the jellyfish *Aequorea victoria*

green fluorescent protein (gfp) in human cell line 293 as well as *in vivo*, the change in codon usage within the gfp coding sequence is required because a set of isoacceptor tRNAs in human cells is different from that used in jellyfish (see abstract). Additionally, Kim et al. also teach that in order to achieve high-level expression of heterologous gene in mammalian cells, codon optimization for the heterologous gene is required because codon bias has been observed in many species (see abstract).

Accordingly, it would have been obvious for an ordinary skilled artisan to further modify the composition taught by Krieg et al. and Carson et al. by modify the nucleic acid sequences encoding a plant allergen such as Amb al ragweed allergic proteins or peptides by substituting codon bases of these nucleic acid sequences with analogous codon bases commonly used cells of treated subjects (mammals and including human) in light of the teachings of Zolotukhin et al., Kim et al.

One of ordinary skill in the art would have been motivated to carry out the above modification to attain an efficient and high expression of non-secreted Amb a1 ragweed allergic proteins or peptides in antigen presenting cells (APCs) in the tissues of treated hosts, so that they are available to activate the desired allergen-specific Th1 lymphocytes.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claims are allowed.

Claims 2-3, 5, 23-24 and 27-28 are objected because they are dependent on rejected claims. However, they would be allowable if they are rewritten in independent formats and drawn to the elected invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to LIE, Zeta Adams, whose telephone number is (703) 305-3291.

Quang Nguyen, Ph.D.

Gerald A. Leffers Jr.
PATENT EXAMINER
A.U. 1636